Form PTO 1390 (REV 5-93) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER P50972
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED / ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5) 10/030718
INTERNATIONAL APPLICATION NO. PCT/US00/21394	INTERNATIONAL FILING DATE 4 August 2000	PRIORITY DATE CLAIMED 6 August 1999
TITLE OF INVENTION METHOD FOR PREPARING CYCLOHEXANE CARBOXYLIC ACIDS		
APPLICANT(S) FOR DO/EO/US Ann M. DIEDERICH, Ann Marie ELDRIDGE, Robert J. MILLS, Vance J. NOVAK		

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1 [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.

2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.

3. [X] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).

4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] has been transmitted by the International Bureau.
   c. [X] is not required, as the application was filed in the United States Receiving Office (RO/US).

6. [ ] A translation of the International Application into English (35 U.S.C. 371(c)(2)).

7. [ ] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.

8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S. C. 371(c)(3)).

9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).

10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. [X] An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98; and Form PTO-1449.

12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. 3.28 and 3.31 is included.

13. [X] A FIRST preliminary amendment.

14. [ ] A SECOND or SUBSEQUENT preliminary amendment.

15. [X] Please amend the specification by inserting before the first line the sentence: This is a §371 national stage entry of International Application PCT/US00/21434, filed 4 August 2000, which claims benefit from the following Provisional Application: 60/147,578 filed 6 August 1999.

16. [ ] A substitute specification.

17. [ ] A change of power of attorney and/or address letter.

18. [x] An Abstract on a separate sheet of paper.

19. [ ] Other items or information:

US APPLICATION NO. (if known, see 37 CFR 1.50)	INTERNATIONAL APPLICATION NO.	ATTORNEYS DOCKET NO.
10/030718	PCT/US00/21394	P50972

20. [X] The following fees are submitted:				CALCULATIONS	PTO USE ONLY
Basic National Fee (37 C.F.R. 1.492(a)(1)-(5)):					
Search Report has been prepared by the EPO or JPO **$890.00**					
International Preliminary Examination Fee paid to USPTO (37 CFR 1.492) **$710.00**				**$710.00**	
No International Preliminary Examination Fee paid to USPTO (37 CFR 1.492) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) **$740.00**					
Neither International Preliminary Examination Fee (37 CFR 1.492) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO.....**$1,040.00**					
International Preliminary Examination Fee paid to USPTO (37 CFR 1.492) and all claims satisfied provisions of PCT Article 33(2)-(4).....**$100.00**					
ENTER APPROPRIATE BASIC FEE AMOUNT =				**$710.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				**$0.00**	
Claims	Number Filed	Number Extra	Rate		
Total claims	**19 - 20 =**	**0**	**0 x $18.00**	**$0.00**	
Independent claims	**5 - 3 =**	**2**	**2 x $84.00**	**$168.00**	
Multiple dependent claims (if applicable)			**+ $280.00**	**$0.00**	
TOTAL OF ABOVE CALCULATIONS =				**$878.00**	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				**$**	
SUBTOTAL =				**$878.00**	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)) +				**$**	
TOTAL NATIONAL FEE =				**$878.00**	
				Amount to be refunded	$
				charged	**$878.00**

a. ☐ A check in the amount of $____ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. 19-2570 in the amount of **$878.00** to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-2570 . A duplicate copy of this sheet is enclosed.

d. ☒ General Authorization to charge any and all fees under 37 CFR 1.16 or 1.17, including petitions for extension of time relating to this application (37 CFR 1.136 (a)(3)).

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:
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PATENT
ATTORNEY'S DOCKET NUMBER **P50972**

TRANSMITTAL LETTER TO THE U.S. DESIGNATED OFFICE
(DO/US) - ENTRY INTO NATIONAL STAGE UNDER 35 USC 371

INTERNATIONAL APP. NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/US00/21434	**4 August 2000**	**6 August 1999**

TITLE OF INVENTION
Method for Preparing Cyclohexane Carboxylic Acids

APPLICANT(S) FOR DO/US
Ann M. DIEDERICH, Ann Marie ELDRIDGE, Robert J. MILLS, Vance J. NOVAK

Box PCT
Commissioner of Patents and Trademarks
Washington, D.C. 20231
ATTENTION: DO/US

PRELIMINARY AMEMDMENT

Dear Sir:

Preliminary to calculation of the filing fees and examination of the above noted application, entrance of the following remarks and amendments into the record is respectfully requested.

In the Claims:

Please amend the following claims:

REMARKS

This Preliminary Amendment is being made upon entry of International Application No. PCT/US00/21434 in the U.S. §371 national phase of prosecution.

Please amend the claims as follows:

4. The process of any one of claims 1 wherein n in R_n is 2 and one group is substituted on at the 3 position and the other group is substituted on the 4 position.

5. The process of any one of claims 1 wherein R_1 is methyl, one of R_n is methoxy, -O-CF_3, -O-CHF_2, or -O-CH_2CHF_2 and the other is C_{4-6}cycloalkyloxy.

6. The process of any one of claim 1 wherein n in R_n is 2 and one is 3-cyclopentyloxy and a second Rn group is 4-methoxy.

9. A compound according to any one of claims 7 wherein n in R_n is 2 and one is 3-cyclopentyloxy and a second R_n group is 4-methoxy.

12. A compound according to claim 10 wherein n in R_n is 2 and one is 3-cyclopentyloxy and the second R_n group is 4-methoxy.

15. A compound according to claim 13 wherein n in R_n is 2 and one is 3-cyclopentyloxy and a second Rn group is 4-methoxy.

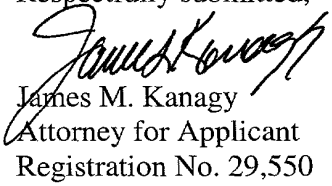
19. A compound according to claim 17 wherein n in R_n is 2 and one is 3-cyclopentyloxy and the second is 4-methoxy.

A marked version of the amended claims accompanies this paper.

An abstract on a separate sheet of paper accompanies this request.

Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is encouraged to call the undersigned at the number below. If any additional fees or charges are required by this paper the Commissioner is hereby authorized to charge Deposit account 19-2570 accordingly.

Respectfully submitted,



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MARKED UP VERSION OF CLAIMS TO SHOW CHANGES MADE

4. The process of any one of claims 1 ~~-3~~ wherein n in R_n is 2 and one group is substituted on at the 3 position and the other group is substituted on the 4 position.

5. The process of any one of claims 1~~-4~~ wherein R_1 is methyl, one of R_n is methoxy, -O-CF_3, -O-CHF_2, or -O-CH_2CHF_2 and the other is C_{4-6}cycloalkyloxy.

6. The process of any one of claim 1~~-5~~ wherein n in R_n is 2 and one is 3-cyclopentyloxy and a second Rn group is 4-methoxy.

9. A compound according to any one of claims 7 ~~-or 8~~ wherein n in R_n is 2 and one is 3-cyclopentyloxy and a second R_n group is 4-methoxy.

12. A compound according to claim 10 ~~or 11~~ wherein n in R_n is 2 and one is 3-cyclopentyloxy and the second R_n group is 4-methoxy.

15. A compound according to claim 13 ~~or 14~~ wherein n in R_n is 2 and one is 3-cyclopentyloxy and a second Rn group is 4-methoxy.

19. A compound according to claim 17 ~~or 18~~ wherein n in R_n is 2 and one is 3-cyclopentyloxy and the second is 4-methoxy.

ABSTRACT

This invention relates to a method for preparing 4-substituted-4-cyanocyclohexane carboxylates by forming the cyclohexane ring by treating a α,α-bis(2-haloethyl)-4-benzeneacetonitrile with a dialkyl malonate and decarboxylating the resulting diester.

Method For Preparing Cyclohexane Carboxylic Acids

Area of the Invention

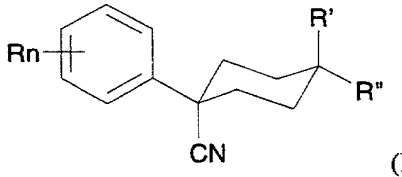
This invention relates to a method for preparing 4-substituted-4-cyanocyclohexancarboxylic acids. Exemplary compounds are useful as PDE 4 inhibitors.

Background of the Invention

The process of this invention relates to making compounds which are useful in treating diseases modulated by the isoforms of the phosphodiesterase 4 enzyme. The novel intermediates and processes of this invention are useful in making acids which are known PDE 4 inhibitors. They are useful for, among other things, treating pulmonary diseases such as chronic obstructive pulmonary disease (COPD) and asthma. The compounds which are prepared by the methods of this invention are described in, for example U.S. patent 5,554,238 issued 03 September, 1996. That patent is incorporated here by reference in full. Those compounds, particularly the 4-cyanocyclohexanoic acids, have marked effects on neutrophil activity, inhibiting neutrophil chemotaxis and degranulation *in vitro*. In animal models, those compounds reduce neutrophil extravasation from the circulation, pulmonary sequestration and the edematous responses to a number inflammatory insults *in vivo*. They have been found to be useful in treating COPD in humans, and possibly in other mammalian species which suffer from COPD.

Summary of the Invention

In a first aspect, this invention relates to a process for preparing a compound of formula (I)



(I)

where

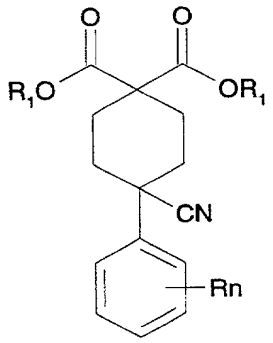
R is halo, C_{1-6}alkyl, C_{1-6}alkyl substituted with 1 to 4 halogens, C_{1-6}alkoxy, C_{1-6}alkenyl, -O-$(CH_2)_m$cycloalkyl of 3-6 carbons;

n is 1-5;

m is 0 - 6; and

R' and R" are independently hydrogen or CO(O)X where X is hydrogen or C_{1-6}alkyl;

which process comprises decarboxylating the diester or diacid of Formula (A)



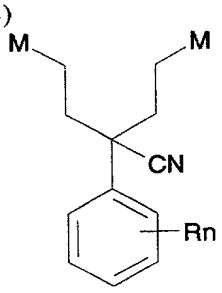
(A)

where R_1 is hydrogen or a C_{1-6}alkyl-ester forming group and R and n are the same as for Formula (I).

In a further aspect this invention relates to a compound of formula (A) per se.

In a third aspect this invention relates to preparing certain other intermediates that are useful in preparing the diester or di-acid of Formula (A), and the intermediates themselves, i.e:

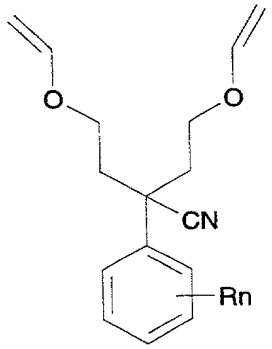
a compound of Formula (B)



(B)

wherein R and n are the same as in Formula (I) and M is OH, an activated hydroxyl group, or halo; and

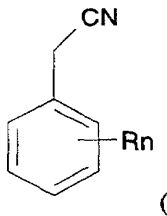
a compound of Formula (C)



(C)

wherein R and n are the same as in Formula (I).

In yet another aspect, the invention provides a method for making a compound of Formula (C) by treating the nitrile of formula (D)

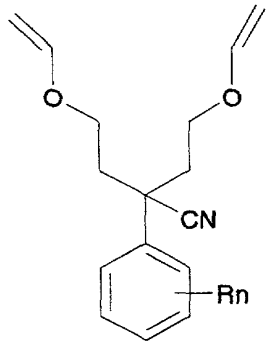


(D)

where R and n are the same as defined above, with 2-chloroethyl vinyl ether and a strong base.

This invention also provides a method for preparing a compound of Formula (I) which comprises

a. converting the vinylethyl ether of Formula (C)



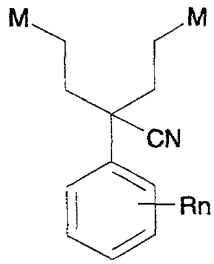
(C)

wherein R and n are halo, C_{1-6}alkyl, C_{1-6}alkyl substituted with 1 to 4 halogens, C_{1-6}alkoxy, C_{1-6}alkenyl, -O-$(CH_2)_m$cycloalkyl of 3-6 carbons;

n is 1-5;

m is 0 - 6;

to a compound of Formula (B)



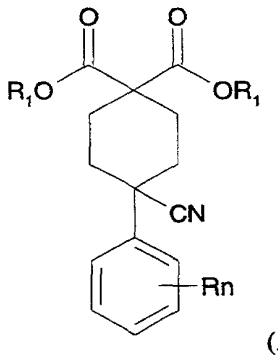
(B)

where M is OH,

b. converting the hydroxyl group of Formula (B) to a compound of Formula (B) where M is a tosylate, mesylate or a triflate,

c. converting the tosylate, mesylate or triflate in Formula (B) to a compound of Formula (B) where M is halo,

d. treating the di-halo compound with dialkyl malonate to obtain a compound of Formula (A)



(A)

where R_1 is lower alkyl,

e. optionally saponfying the diester of Formula (A) to obtain a compound of Formula (A) where R_1 is hydrogen; and

f. decarboxylating a compound of Formula (A) where R_1 is hydrogen or C_{1-6}alkyl to obtain a compound for Formula (I) where one of R' is hydrogen and the other is CO(O)X where X is C_{1-6}alkyl or hydrogen.

Specific Embodiments of the Invention

This invention provides a method for preparing cyclohexanoic acids. In particular it provides an alternative means for preparing the cyclohexanoic acids disclosed in U.S. patent 5,554,238 where the 4-position on the cyclohexane ring has a CN group.

"Halo" as used herein includes fluoro, chloro, bromo, and iodo. "Halide" includes fluoride, chloride, bromide and iodide.

For all of the compounds disclosed herein, a preferred embodiment is one where there are two R groups, i.e. n is 2. Most preferred are those compounds where one R group is at the 3 position and the second R group is on the 4 position of the benzene ring. More particularly it is preferred that each R group be independently C_{4-6}cycloalkyloxy or C_{1-2}alkoxy unsubstituted or substituted by 1 or more halogens. More preferred are methoxy, C_{1-2}alkoxy substituted by up to 3 fluoro atoms, cyclopropylmethoxy or cyclopentyloxy. The more preferred R groups are those wherein the 4-position R group is methoxy, -O-CF_3, -O-CHF_2, or -O-CH_2CHF_2. and the 3-position R group is cyclopropylmethoxy or cyclopentyloxy.

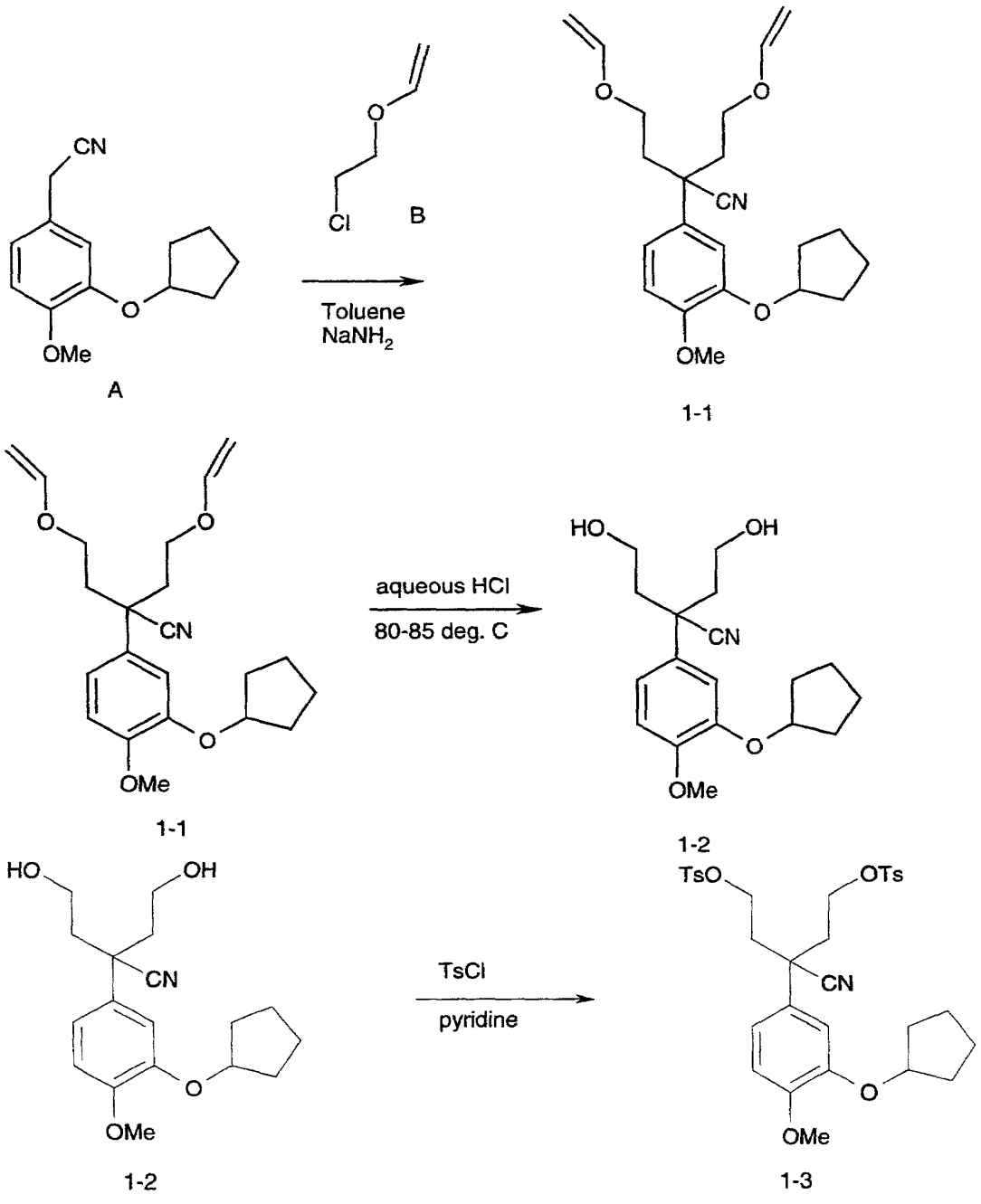
In Formula (A) the most preferred R_1 groups are hydrogen, methyl or ethyl.

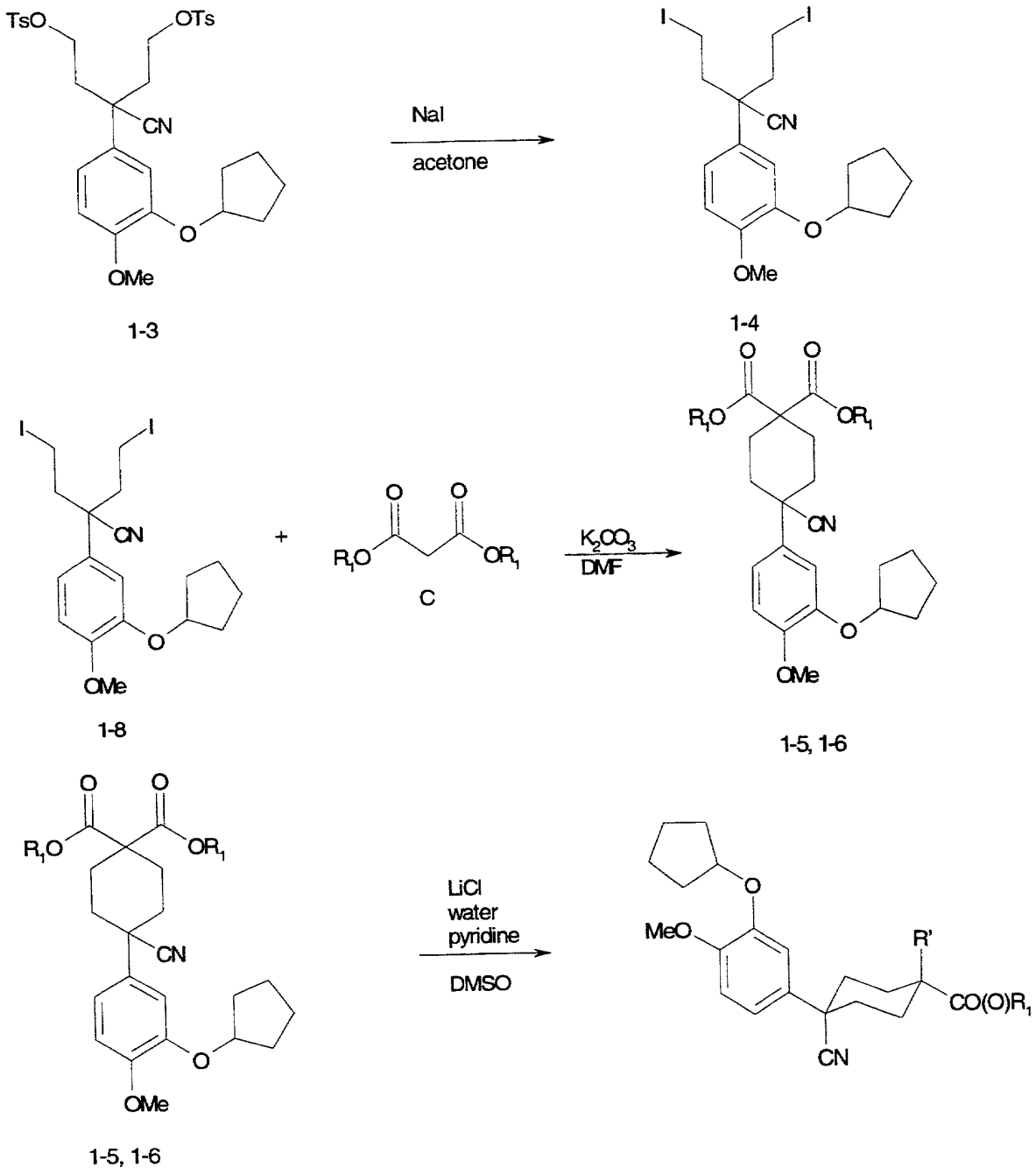
In Formula (B) the most preferred M groups are OH, tosyl and iodo.

The most preferred product of the process of this invention are those compounds which have a 3-cyclopentyloxy-4-methoxyphenyl substitution pattern.

Reaction Scheme I provides a diagrammatic overview of the intermediates and chemistries employed in this invention.

Scheme I





The starting material 3-cyclopentyloxy-4-methoxybenzeneacetonitrile is a known compound. See for example U.S. patent 5,449,686. The 2-chloroethylvinyl ether is commercially available (Aldrich). To effect the reaction, a strong base is charged to a reaction vessel containing a suitable non-polar solvent to which the vinyl ether is added. This mixture is heated to between about 30 to 70 °C and charged with the benzeneacetonitrile (A) pre-dissolved in the same solvent as the base and the vinyl ether.

Toluene is a preferred solvent. A preferred base is sodium amide. The amount of base is equivalent, on a molar basis, to that of the vinyl ether. Both are used in about a three-fold excess relative to the substrate. After the benzeneacetonitrile has been charged to the reaction flask, the solution is further heated to around 80 °C more or less. Usually the reaction is complete in about 30 minutes to 2 hours. The product (1-1) is isolated using standard procedures.

The bis 2-hydroxyethyl compound (1-2)is prepared by treating the vinyl ether moiety prepared as per the preceding paragraph with a strong mineral acid in an aqueous solvent. For example water can be added to the 2-(ethenyloxy)ethyl compound (1-1), heating that combination to about 70-90 °C and then adding a molar excess of a mineral acid such as HCl or the like. A preferred set of conditions is one where the 2-(ethenyloxy)ethyl is treated with water and heated to about 80 °C more or less followed by the addition of a 50% molar excess of concentrated HCl. Under these conditions the reaction is complete in 5 - 20 minutes.

To obtain the halogenated compound 1-4, the diol is converted to a group which can be displaced by a halide ion. For example the diol can be converted to a tosylate, mesylate, or the like, by treating the diol with reagents and under conditions which form the tosylate, etc. By way of example the diol is dissolved in an organic solvent and treated with an excess of *p*-toluenesulfonyl chloride at room temperature for 3- 7 hours. Preferably the reaction is run in pyridine with about a 2.5 molar excess of the *p*-toluenesulfonyl chloride.

This tosylate (or mesylate, triflate, etc) (1-3) is converted to the di-halo 1-4 by dissolving it in a polar aprotic solvent, and adding a weak base and a halide salt. This mixture is heated to reflux for a number of hours, for example overnight. A preferred solvent is acetone or dimethyl formamide. A preferred halide salt is sodium or lithium iodide though other sodium or potassium salts of fluorine, chlorine and bromine can be used as well. A 2 to 6-fold excess of the halide salt is preferred. Refluxing overnight usually effects completion of the reaction.

Forming the cyclohexane dicarboxylates or diacids 1-5 and 1-6 is effected by charging the di-halo compound (1-4) to a solution of a dialkyl malonate or malonic acid and a weak base in a dipolar aprotic solvent. This slurry is stirred for an extended period of time at an elevated temperature, for example overnight. More specifically sodium or potassium carbonate is combined with the likes of dimethyl malonate in a solvent such as dimethylformamide. Then the di-halo 1-4 is added and the resulting slurry is stirred overnight at about 75-95 °C or so. The malonate is added in about a 1:1molar ratio to that of the di-halo compound.

The diester may be saponified to give the diacid, though this step is not illustrated in Scheme 1. This is accomplished by treating the diester with an aqueous base in a water-

miscible solvent. For example the diester is charged to a reaction vessel containing the likes of tetrahydrofuran to which is added water and an alkali hydroxide base such as lithium hydroxide. This solution is heated at reflux for a number of hours, for example overnight.

Decarboxylating the diester or dicaid to get the mono-ester or mono-acid is accomplished by dissolving the diester in the likes of dimethylsulfoxide, adding about an equivalent of a base such as pyridine, about 3 equivalents of water and about 3 equivalents of a salt such as lithium chloride. This solution is stirred for several hours at 100 to 150 °C or thereabouts for 4-8 hours. Product is extracted from an acidified aqueous solution and further purified by conventional means. The product is a mixture of cis and trans isomers in about a 1:1 ratio. The *cis* form of the ester or acid can be enriched by dissolving a mixture of isomers in a lower alkanol and treating that solution with the alkali metal salt of the alkanol. A preferred alkanol is *t*-butanol and a preferred alkali metal salt is potassium *t*-butanol. The acid may be obtained by saponifying the ester using a base and then acidifying the resulting salt with using a mineral acid, for example.

The following examples are provided to illustrate the invention. These illustrative examples are not intended to limit the claimed invention in any fashion.

Examples

Example 1

Preparation of 3-(Cyclopentyloxy)-α,α-bis[2-(ethenyloxy)ethyl]-4-methoxybenzeneacetonitrile

A 1 L flask was charged with 150 mL of toluene, sodium amide (16.5 g, 0.38 mole, 2.9 equivalents), and 2-chloroethyl vinyl ether (41.9 g, 0.39 mole, 3.0 equivalents). The suspension was heated to 50 °C, then charged with a solution of 3-cyclopentyloxy-4-methoxybenzeneacetonitrile (30 g, 0.13 mole, 1.0 equivalents) in 150 mL of toluene. The reaction was then carefully heated to 80 °C. The progress was followed by HPLC (acetonitrile/0.1 N aqueous ammonium acetate at 65/35, 15 cm Beckman ODS Ultrasphere, 2 mL/min, 215 nm UV). After 60 minutes, the solution was poured into 1 L of water and 300 mL of t-butyl methyl ether. The layers were separated, the organic layer washed with water, then brine. The solvent was removed under reduced pressure to give a brown oil (52.1 g). The captioned compound was isolated by column chromatography (230-400 mesh silica gel, 10/1 hexane/ethyl acetate).

Mass spectrometry gave m/z = 372 $(M+H^+)^+$

(^{1}H NMR, 300 MHz, $CDCl_3$, δ ppm) δ 1.55-1.65 (m, 2H, ring CH_2), δ 1.70-2.00 (m, 6H, ring CH_2's), δ 2.2-3.5 (m, 4 H,$(CH_2)_2CCN$), δ 3.50-3.85 (m, 4H, CH_2O), δ 3.85 (s, 3H, OCH_3), δ 3.95-4.10 (m. 4H, CH_2 alkene), δ 4.8 (m, 1H, ring CH), δ 6.30-6.40 (m, CH, alkene), δ 6.85-7.0 (m, 3H, aromatic)

Example 2

Preparation of 3-(Cyclopentyloxy)-α,α-bis(2-hydroxyethyl)-4-methoxybenzeneacetonitrile

Purified 3-(cyclopentyloxy)-α,α-bis[2-(ethenyloxy)ethyl]-4-methoxybenzeneacetonitrile (5 g, 13.5 mmol) was treated with water (50 mL) and heated to 80 °C with rapid stirring. Concentrated hydrochloric acid (1.85 mL, 22.2 mmol) was added and stirring was continued for 10 minutes. The solution was poured into ice water (50 mL) and methylene chloride (50 mL). The layers were separated, and the aqueous layer was extracted once with methylene chloride. The combined organic layers were washed with water, then brine, and concentrated to a light yellow oil in quantitative yield. Structure and purity were confirmed by ^{1}H NMR.

(^{1}H NMR, 300 MHz, $CDCl_3$, δ ppm) δ 1.55-1.70 (m, 2H, ring CH_2), δ 1.75-1.95 (m, 6H, ring CH_2's), δ 2.10-2.40 (m, 4H, $(CH_2)_2CCN$), δ 3.55-3.85 (m, 4H, CH_2O), 3.88 (s, 3H, OMe), δ 4.8 (m, 1H, ring CH), δ 6.80-7.00 (m, 3H, aromatic)

Example 3

Preparation of 3-(Cyclopentyloxy)-4-methoxy-α,α-bis[2-[[(4-methylphenyl)sulfonyl]oxy]ethyl]benzeneacetonitrile

A 250 mL flask was charged with 3-(cyclopentyloxy)-α,α-bis(2-hydroxyethyl)-4-methoxybenzeneacetonitrile (6.4 g, 20.1 mmol), pyridine (65 mL), and *p*-toluenesulfonyl chloride (9.56 g, 50.2 mmol). The solution warmed slightly (exothermic), then was stirred at room temperature for 5 hours. The reaction was deemed complete by HPLC (acetonitrile/0.1 N aqueous ammonium acetate at 65/35, 15 cm Beckman ODS Ultrasphere, 2 mL/min, 215 nm UV). The reaction was poured into 100 mL of 5% HCl and 50 mL of methylene chloride. The layers were separated, and the organic layer was washed with 5% HCl until neutral. The neutralized organic layer was then washed once with brine and concentrated. The captioned compound was isolated as a white solid by crystallization from ethanol and t-butyl methyl ether.

Mass spectrometry gave m/z = 645 $(M+NH_4^+)^+$

(^{1}H NMR, 300 MHz, $CDCl_3$, δ ppm) δ 1.55-1.70 (m, 2H, ring CH_2), δ 1.72-2.0 (m, 6H, ring CH_2's), δ 2.20-2.45 (m, 4H, $(CH_2)_2CCN$), 2.45 (s, 3H, ar-CH_3), 3.85 (s, 3H, OMe), δ 3.85-4.28 (m, 4H, CH_2O), δ 4.75 (m, 1H, ring CH), δ 6.75-7.75 (11H indicated, aromatic)

Example 4

Preparation of 3-(Cyclopentyloxy)-α,α-bis(2-iodoethyl)-4-methoxybenzeneacetonitrile

A 250 mL flask was charged with 3-(cyclopentyloxy)-4-methoxy-α,α-bis[2-[[(4-methylphenyl)sulfonyl]oxy]ethyl]benzeneacetonitrile (5.0 g, 7.97 mmol), acetone (75 mL), and sodium bicarbonate (50 mg). This solution was stirred well while sodium iodide (5.98 g, 39.9 mmol) was added, then heated to reflux overnight. The reaction was poured into

aqueous ammonium chloride and sodium bisulfite, then extracted with t-butyl methyl ether. The organic layer was dried over sodium sulfate, then concentrated to a clear colorless oil. The captioned compound was crystallized from t-butyl methyl ether and hexanes to give a white solid.:

Mass spectrometry gave m/z = 540 $(M+H^+)^+$

CHN analysis calculated for $C_{18}H_{23}NO_2I_2$ (539.12): C 40.10, H 4.30, N 2.60; found: C 40.06, H 4.30, N, 2.45.

(^{1}H NMR, 300 MHz, $CDCl_3$, δ ppm) δ 1.55-1.70 (m, 2H, ring CH_2), δ 1.75-2.05 (m, 6H, ring CH_2's), δ 2.35-2.62 (m, 4H, $(CH_2)_2CCN$), δ 2.8 (m, 2H, CH_2I), δ 3.15 (m, 2H, CH_2I), 3.87 (s, 3H, OMe), δ 4.8 (m, 1H, ring CH), δ 6.85 (s, 1H, aromatic), δ 7.18-7.30 (m, 2H, aromatic)

Example 5

Preparation of Dimethyl 4-cyano-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-1,1-cyclohexanedicarboxylate and Diethyl 4-cyano-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-1,1-cyclohexanedicarboxylate

A 125 mL flask was charged with 60 mL of dimethylformamide, potassium carbonate (5.02 g, 36.4 mmol, 3.6 equivalents), dimethylmalonate (1.33 g, 10.1 mmol. 1.0 equivalents), and then 3-(cyclopentyloxy)-α,α-bis(2-iodoethyl)-4-methoxybenzeneacetonitrile (6.0 g, 11.1 mmol, 1.1 equivalents). The slurry was stirred at 80 °C overnight. The completed reaction was poured into 50 mL of water and 50 mL of *t*-butyl methyl ether. The organic layer was extracted three times with water, then once with brine. The product was isolated by column chromatography (Flash silica [230-400 mesh], 80/20 hexanes/ethyl acetate). Alternatively it was crystallized from hexanes/ethyl acetate (3/1) to give white crystals. The diethyl derivative was prepared using the same procedure.

Dimethyl ester:

Mass spectrometry gave m/z = 416 $(M+H^+)^+$

CHN analysis calculated for $C_{23}H_{29}NO_6$ (539.12): C 66.49, H 7.04, N 3.37; found: C 66.24, H 6.94, N, 3.33.

(^{1}H NMR, 300 MHz, $CDCl_3$, δ ppm) δ 1.55-1.67 (m, 2H, ring CH_2), δ 1.75-2.60 (m, 14H, ring CH_2's), 3.75 (s, 3H, CO_2Me), 3.78 (s, 3H, CO_2Me), 3.82 (s, 3H, OMe), δ 4.8 (m, 1H, ring CH), δ 6.80-7.02 (m, 3H, aromatic)

Diethyl ester

Mass spectrometry gave m/z = 444 $(M+H^+)^+$

mp. 74.0-74.5

(^{1}H NMR, 300 MHz, $CDCl_3$, δ ppm) δ 1.20-1.38 (m, 6H, ethyl CH_3), δ 1.50-2.60 (m, 16H, ring CH_2's), 3.85 (s, 3H, OMe), δ 4.65-4.85 (m, 4H, ethyl CH_2), δ 4.8 (m, 1H, ring CH), δ 6.80-7.05 (m, 3H, aromatic).

Example 6

Hydrolysis of the diethyl ester to the diacid

A 25 mL flask was charged with tetrahydrofuran (5 mL), the diethyl ester (SB 220523, 0.5 g, 1.13 mmol, 1.0 equivalent), water (5 mL), and lithium hydroxide monohydrate (0.95 g, 22.6 mmol, 20 equivalents). The solution was stirred at reflux for 18 hours. The reaction was deemed complete by HPLC (15 cm Supelcocil LC-ABZ, 40/60/0.1 [acetonitrile/water/TFA], 1.5 mL/min., 215 nm UV).The reaction solution was then cooled and diluted with 10% HCl and t-butyl methyl ether. The layers were separated and the aqueous layer was washed once with t-butyl methyl ether. The organic layers were combined and washed with water and then brine. The solution was then concentrated to a tan solid. Water was removed by reconcentrating once with acetonitrile. The crude product was obtained in about 90% yield. The crude product showed residual ethyl ester (< 5%) by HPLC and ^{1}H NMR.

(^{1}H NMR, 300 MHz, $CDCl_3$, δ ppm) δ 1.55-1.70 (m, 2H, ring CH_2), δ 1.75-2.35 (m, 12H, ring CH_2's), δ 2.52-2.63 (m, 2H, ring CH_2), 3.85 (s, 3H, OMe), δ 4.8 (m, 1H, ring CH), δ 6.8-7.0 (m, 3H, aromatic)

Example 7

Decarboxylation of the diester: Ethyl 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)-cyclohexanecarboxylate

A 100 mL flask was charged with dimethylsulfoxide (35 mL), dimethyl 4-cyano-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-1,1-cyclohexanedicarboxylate (3.5 g, 8.43 mmol, 1.0 equivalent), water (0.455 g, 25,3 mmol, 3.0 equivalents), pyridine (0.66 g, 8.43 mmol, 1.0 equivalent), and lithium chloride (1.07 g, 25.3 mmol, 3.0 equivalents). The solution was stirred at 130 °C for 6.5 hours. The reaction solution was then cooled and diluted with 1% HCl and t-butyl methyl ether. The layers were separated and the organic layer was washed with water twice and with brine once. The solution was concentrated to a clear oil. Water was removed by reconcentrating once with methanol. The product was obtained in quantitative yield as a clear oil and as a mixture of *cis* and *trans* isomers in about a 1:1 ratio.

Mass spectrometry gave m/z = 372 $(M+H^+)^+$

(^{1}H NMR, 300 MHz, $CDCl_3$, δ ppm) δ 1.29 (t, 3H, ethyl CH_3), δ 1.55-1.70 (m, 2H, ring CH_2), δ 1.75-2.30 (m, 14H, ring CH_2's), δ 2.75-2.80 (m, 1H, $CHCO_2Et$), 3.85 (s, 3H, OMe), δ 4.13-4.22 (q, 2H, ethyl CH_2), δ 4.8 (m, 1H, ring CH), δ 6.8-7.0 (m, 3H, aromatic)

Example 8

Preparation of 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)-cyclohexanecarboxylic acid

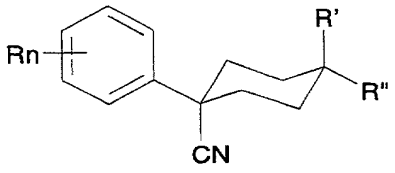
The isomeric mixture (approximately 1 to 1 ratio) of the methyl esters prepared in Example 5 (2.94 g, 8.2 mmol, 1.0 equivalent) was dissolved in *t*-butanol (30 mL) under a nitrogen atmosphere. Potassium *t*-butoxide (1.8 g, 16.5 mmol, 2.0 equivalent) was added

and the mixture was stirred 6-18 hours to give a ratio of *cis* to *trans* isomers of 14 to 1. The same procedure was used to treat the ethyl esters and gave a ratio of 8 to 1. The ratios were monitored using HPLC (15 cm Supelcocil LC-ABZ, 40/60/0.1 [acetonitrile/water/TFA], 1.5 mL/min., 215 nm UV).

To hydrolyze the equilibrated ester product, two drops of water were added to the reaction solution and the solution was stirred until no ester could be detected. The reaction was then diluted with *t*-butyl methyl ether and 5% HCl (the pH of the aqueous layer was between 1-2). The layers were separated and the organic layer was washed with brine. The ratio of *cis* to *trans* acid was improved even further (to 121 to 1) by crystallizing the *cis/trans* misture from 20 ml of hexanes/ethyl acetate (3/1)

Claims

1. A process for preparing a compound of formula (I)



(I)

where

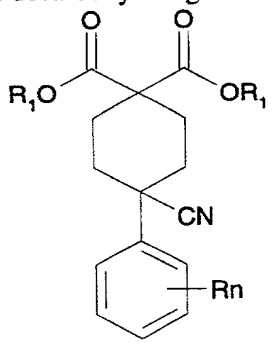
R is halo, C_{1-6}alkyl, C_{1-6}alkyl substituted with 1 to 4 halogens, C_{1-6}alkoxy, C_{1-6}alkenyl, -O-$(CH_2)_m$cycloalkyl of 3-6 carbons;

n is 1-5;

m is 0 - 6; and

R' and R" are independently hydrogen or CO(O)X where X is hydrogen or C_{1-6}alkyl;

which process comprises decarboxylating the diacid or diester of Formula (A)



(A)

where R_1 is hydrogen or C_{1-6} alkyl-ester forming group of 1-6 carbon atoms and R and n are the same as for Formula (I).

2. The process of claim 1 wherein the diester or diacid is combined with about 1 equivalent of a base, about 3 equivalents of water and about 3 equivalents of an alkali salt in a suitable solvent and heated to between about 100 to 150 °C for about 4-8 hours.

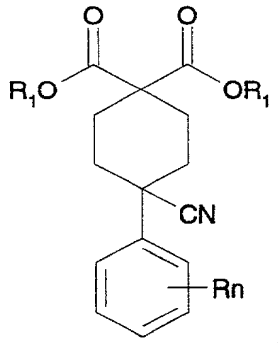
3. The process of claim 1 wherein R_1 is hydrogen, methyl or ethyl and the base is pyridine and the salt is lithium chloride.

4. The process of any one of claims 1 - 3 wherein n in R_n is 2 and one group is substituted on at the 3 position and the other group is substituted on the 4 position.

5. The process of any one of claims 1-4 wherein R_1 is methyl, one of R_n is methoxy, -O-CF_3, -O-CHF_2, or -O-CH_2CHF_2 and the other is C_{4-6}cycloalkyloxy.

6. The process of any one of claim 1-5 wherein n in R_n is 2 and one is 3-cyclopentyloxy and a second Rn group is 4-methoxy.

7. A compound of formula (A)



(A)

wherein

R is halo, C_{1-6}alkyl, C_{1-6}alkyl substituted with 1 to 4 halogens, C_{1-6}alkoxy, C_{1-6}alkenyl, -O-$(CH_2)_m$cycloalkyl of 3-6 carbons;

n is 1-5;

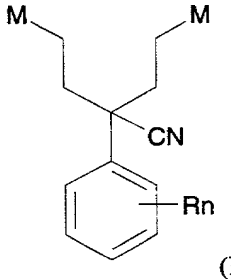
m is 0 - 6;

R_1 is hydrogen or a C_{1-6} alkyl-ester forming group of 1-6 carbon atoms.

8. A compound according to claim 7 wherein n in R_n is 2 and R_n is methoxy, -O-CF_3, -O-CHF_2, or -O-CH_2CHF_2 and the other is C_{4-6}cycloalkyloxy.

9. A compound according to any one of claims 7 or 8 wherein n in R_n is 2 and one is 3-cyclopentyloxy and a second R_n group is 4-methoxy.

10. A compound of Formula (B)



(B)

wherein

R is halo, C_{1-6}alkyl, C_{1-6}alkyl substituted with 1 to 4 halogens, C_{1-6}alkoxy, C_{1-6}alkenyl, -O-$(CH_2)_m$cycloalkyl of 3-6 carbons;

n is 1-5;

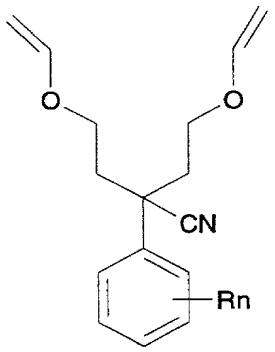
m is 0 - 6; and

M is OH, an activated hydroxyl group, or halo.

11. A compound according to claim 10 wherein n in R_n is 2 and R_n is methoxy, -O-CF_3, -O-CHF_2, or -O-CH_2CHF_2 and the other is C_{4-6}cycloalkyloxy.

12. A compound according to claim 10 or 11 wherein n in R_n is 2 and one is 3-cyclopentyloxy and the second R_n group is 4-methoxy.

13. A compound of Formula (C)



(c)

wherein

R is halo, C_{1-6}alkyl, C_{1-6}alkyl substituted with 1 to 4 halogens, C_{1-6}alkoxy, C_{1-6}alkenyl, -O-$(CH_2)_m$cycloalkyl of 3-6 carbons;

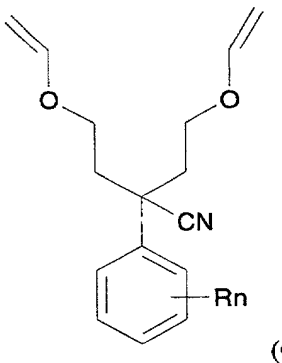
n is 1-5; and

m is 0 - 6.

14. A compound according to claim 13 wherein n in R_n is 2 and R_n is methoxy, -O-CF_3, -O-CHF_2, or -O-CH_2CHF_2 and the other is C_{4-6}cycloalkyloxy.

15. A compound according to claim 13 or 14 wherein n in R_n is 2 and one is 3-cyclopentyloxy and a second Rn group is 4-methoxy.

16. A process for preparing a compound of Formula (C)



(C)

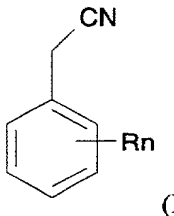
wherein

R is halo, C_{1-6}alkyl, C_{1-6}alkyl substituted with 1 to 4 halogens, C_{1-6}alkoxy, C_{1-6}alkenyl, -O-$(CH_2)_m$cycloalkyl of 3-6 carbons;

n is 1-5; and

m is 0 - 6.

which comprises by treating the nitrile of formula (D)



(D)

with 2-chloroethyl vinyl ether and a strong base

where, in Formula (D):

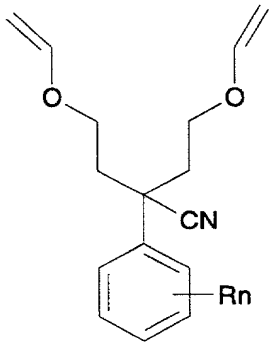
R is halo, C_{1-6}alkyl, C_{1-6}alkyl substituted with 1 to 4 halogens, C_{1-6}alkoxy, C_{1-6}alkenyl, -O-$(CH_2)_m$cycloalkyl of 3-6 carbons;

n is 1-5; and

m is 0 - 6.

17. A process for preparing a compound of Formula (I) according to claim 1, which process comprises

a. converting the vinylethyl ether of Formula (C)



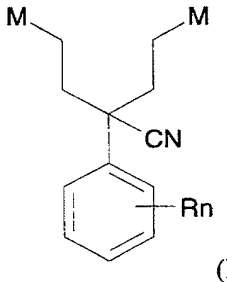
(C)

wherein R and n are halo, C_{1-6}alkyl, C_{1-6}alkyl substituted with 1 to 4 halogens, C_{1-6}alkoxy, C_{1-6}alkenyl, -O-$(CH_2)_m$cycloalkyl of 3-6 carbons;

n is 1-5;

m is 0 - 6;

to a compound of Formula (B)



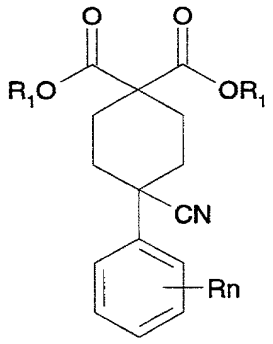
(B)

where M is OH,

b. converting the hydroxyl group of Formula (B) to a compound of Formula (B) where M is a tosylate, mesylate or a triflate,

c. converting the tosylate, mesylate or triflate in Formula (B) to a compound of Formula (B) where M is halo,

d. treating the di-halo compound with dialkyl malonate to obtain a compound of Formula (A)



(A)

where R_1 is lower alkyl,

e. optionally saponfying the diseater of Formula (A) to obtain a compound of Formula (A) where R_1 is hydrogen, and

f. decarboxylating a compound of Formula (A) where R_1 is hydrogen or C_{1-6}alkyl to obtain a compound for Formula (I) where one of R' is hydrogen and the other is CO(O)X where X is C_{1-6}alkyl or hydrogen.

18. The process of claim 17 wherein n in R_n is 2 and R_n is methoxy, -O-CF_3, -O-CHF_2, or -O-CH_2CHF_2 and the other is C_{4-6}cycloalkyloxy, M is tosylate, and thereafter iodo, and R1 is methyl or ethyl.

19. A compound according to claim 17 or 18 wherein n in R_n is 2 and one is 3-cyclopentyloxy and the second is 4-methoxy.

Docket No.: P50972

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

"METHOD FOR PREPARING CYCLOHEXANE CARBOXYLIC ACIDS"

the specification of which (check one)
[ ] is attached hereto.
[X] was filed on **04 August 2000** as Serial No. **PCT/US00/21434**
and was amended on (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below any foreign application for patent or Inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Number	Country	Filing Date	Priority Claimed

I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States provisional application(s) listed below.

Application Number	Filing Date
60/147,578	**06 August 1999**

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

Serial No.	Filing Date	Status

I hereby appoint the practitioners associated with the Customer Number provided below to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith, and direct that all correspondence be addressed to that Customer Number:

Customer Number 20462.

Address all correspondence and telephone calls to **James M. Kanagy**, SmithKline Beecham Corporation, Corporate Intellectual Property-U.S., UW2220, P.O. Box 1539, King of Prussia, Pennsylvania 19406-0939, whose telephone number is 610-270-5014.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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